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Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery

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Abstract: OBJECTIVES: To determine the prevalence, spectrum and course of cerebral lesions in neonates with congenital heart disease (CHD) undergoing full flow cardiopulmonary bypass (CPB) surgery using magnetic resonance imaging (MRI) and to examine the correlation between cerebral lesions and clinical neurological abnormalities. METHODS: Prospective cohort study of neonates with d-transposition of the great arteries (n = 22), univentricular heart malformation with hypoplastic aortic arch (n = 6) and aortic arch obstructions (n = 2) undergoing CPB. Neonates underwent cerebral MRI and blinded standardized neurological examination before (median day 6) and after surgery (day 13). The MRI findings were compared with those of 20 healthy controls. RESULTS: Preoperative cerebral lesions were present in 7 of 30 patients (23%) with isolated mild or moderate white matter injury (WMI) (n = 4), isolated small cerebral stroke (n = 1) and combined WMI and stroke (n = 2). None of the healthy controls had cerebral lesions on MRI. CHD neonates with preoperative cerebral lesions had more neurological abnormalities (P = 0.01) than neonates without cerebral lesions. Low arterial oxygen saturation (P = 0.03) was a risk factor for preoperative cerebral lesions, while balloon atrioseptostomy (P = 0.19) was not. After surgery, preoperative cerebral lesions persisted in 5 of 7 neonates, and 2 neonates (7%) showed signs of additional WMI in their postoperative MRI. CONCLUSIONS: In neonates with severe CHD, WMI was the predominant preoperative finding, while cerebral strokes were less frequent. New postoperative lesions were rare. Preoperative neurological abnormalities correlated with the presence of cerebral lesions on MRI.

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ORIGINAL ARTICLE

Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery

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Abstract

OBJECTIVES: To determine the prevalence, spectrum and course of cerebral lesions in neonates with congenital heart disease (CHD) undergoing full flow cardiopulmonary bypass (CPB) surgery using magnetic resonance imaging (MRI) and to examine the correlation between cerebral lesions and clinical neurological abnormalities.

METHODS: Prospective cohort study of neonates with d-transposition of the great arteries ($n = 22$), univentricular heart malformation with hypoplastic aortic arch ($n = 6$) and aortic arch obstructions ($n = 2$) undergoing CPB. Neonates underwent cerebral MRI and blinded standardized neurological examination before (median day 6) and after surgery (day 13). The MRI findings were compared with those of 20 healthy controls.

RESULTS: Preoperative cerebral lesions were present in 7 of 30 patients (23%) with isolated mild or moderate white matter injury (WMI) ($n = 4$), isolated small cerebral stroke ($n = 1$) and combined WMI and stroke ($n = 2$). None of the healthy controls had cerebral lesions on MRI. CHD neonates with preoperative cerebral lesions had more neurological abnormalities ($P = 0.01$) than neonates without cerebral lesions. Low arterial oxygen saturation ($P = 0.03$) was a risk factor for preoperative cerebral lesions, while balloon atrioseptostomy ($P = 0.19$) was not. After surgery, preoperative cerebral lesions persisted in 5 of 7 neonates, and 2 neonates (7%) showed signs of additional WMI in their postoperative MRI.

CONCLUSIONS: In neonates with severe CHD, WMI was the predominant preoperative finding, while cerebral strokes were less frequent. New postoperative lesions were rare. Preoperative neurological abnormalities correlated with the presence of cerebral lesions on MRI.

Keywords: Developmental outcome • Congenital heart disease • Neuroimaging • White matter injury

INTRODUCTION

Congenital heart disease (CHD) is a common diagnosis with a prevalence of 8 per 1000 live births in Europe requiring open heart surgery in ~10–15% in most severe defects [1]. Complex cardiac cyanotic CHD requires early neonatal cardiopulmonary bypass (CPB) surgery. Over the last decades, survival of neonates with severe CHD has increased substantially due to advances in neonatal intensive care medicine, cardiac surgery and CPB technologies providing early surgical repair with good results regarding myocardial function [2]. Nevertheless, ~50% of all childhood survivors with severe CHD demonstrate neurodevelopmental deficits affecting motor and visuospatial skills but also cognition with persistence throughout adolescence [3–6]. Brain injuries on magnetic resonance imaging (MRI) may be detected already preoperatively [7, 8]. White matter injuries (WMI) have been described to occur in 16% [9] to 30% [10] and cerebral strokes in ~20–25% [7, 10–12] before surgery in neonates with severe CHD. Possible risk factors for preoperative brain injuries include intrauterine and foetal haemodynamic conditions [13], depending on the type of CHD and the consequences for cerebral perfusion, as well as postnatal interventions such as balloon atrioseptostomy (BAS) [11] or the degree of preoperative hypoxia [14].

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Preoperative neurological findings include muscular hypo- or hypertonia, behavioural abnormalities such as feeding problems and poor state regulation [15]. These abnormalities are found to be strongly predictive for neurodevelopmental outcome [16], but have not yet been related to cerebral MRI findings.

The aim of the present study was to determine the prevalence, spectrum and course of brain injuries detected on pre- and post-operative MRI in neonates with CHD in relation to corrective or palliative surgery under CPB. Further, we sought to examine the correlation between cerebral lesions and neurological clinical findings.

METHODS

Study design

This study is part of an ongoing prospective cohort study of timing of cerebral lesions and neurodevelopmental outcome in neonates operated for CHD in comparison with a healthy control group. The study has been approved by the local Ethical Committee. Written informed consent was obtained from the parents or legal guardians.

Patients

Between November 2009 and January 2012 all consecutive neonates hospitalized in our institution with a severe type of CHD requiring cardiac surgery under CPB were asked to participate in the study. All neonates were outborn and were transferred after birth. After consent was obtained, neonates underwent cerebral MRI and neurodevelopmental assessment before and after cardiovascular bypass surgery. Neonates <36 weeks of gestational age (GA) at birth and neonates with clinical suspicion or evidence of genetic malformation syndromes associated with neurodevelopmental disabilities were excluded.

Thirty neonates born (male:female = 22:8) at a median GA of 39.3 (range 36.7–41.9) with a median body weight of 3310 (2560–4270) g could be included. After birth cardiac diagnosis was made by transthoracic echocardiography. Prostaglandin E1 infusion was administered if necessary immediately after birth. Eighteen patients with d-transposition of the great arteries (d-TGA) required BAS due to severe hypoxia (arterial oxygen saturation below 70%) or due to echocardiographic signs of restrictive atrial septal defect. A single dose of Heparin (50 units per kg) was given before BAS.

A control group of 20 healthy term neonates was recruited from the Division of Neonatology of the University Hospital Zurich and prospectively studied between January 2011 and February 2012. Cerebral MRI was performed once during the neonatal period using the same MRI protocol as in neonates with CHD.

Surgery and cardiopulmonary bypass

Cardiac surgery included arterial switch operation or Rastelli operation for patients with d-TGA ($n = 22$), Norwood-type stage I palliation for patients with univentricular heart malformation ($n = 6$) and complex aortic arch reconstruction for patients with interrupted aortic arch or severe transverse arch hypoplasia with coarctation of the aortic arch ($n = 2$). Alpha-stat blood gas management was used for CPB with a pump flow rate of 100–150 ml/kg per min to achieve a mean arterial pressure of 40–50 mmHg. Arterial switch operation was performed under mild-to-moderate hypothermia (nasopharyngeal temperature 32–35°C). Norwood-type stage I palliation was performed under moderate-to-severe hypothermia (nasopharyngeal temperature 22–28°C). We performed regional cerebral perfusion through the brachiocephalic trunk during Norwood-type stage I palliation as well as for aortic arch reconstruction with a pump flow rate maintained at 30–50 ml/kg per min and a target arterial pressure of ∼50 mmHg, measured in the right radial artery. A second arterial perfusion cannula was alternatively used to perfuse the descending aortic territory (through ductal cannulation) and the left carotid territory (through direct cannulation of left carotid ostium).

Intraoperative near infrared spectroscopy monitoring of cerebral tissue perfusion was performed in all patients as well as modified ultrafiltration at the end of CPB.

Cerebral magnetic resonance imaging

MRI studies were performed on a 3.0-T scanner (Signa HDxt, GE Healthcare, Milwaukee, WI, USA) using axial T1-weighted spin-echo sequence [repetition time (TR) = 680 ms; echo time (TE) = 21 ms] with a slice thickness of 2.5 mm, T2-weighted fast-spin-echo sequences in three planes with a slice thickness of 2.5 mm (TR = 5300 ms; TE = 102 ms) and diffusion-weighted imaging (35 gradient directions, b-value = 700 s/mm^2, voxel = 0.8 × 0.8 × 2.5 mm^3).

WMI were defined as focal areas measuring <2 mm of abnormal T1-hyperintensity or of low intensity on T1-weighted images in the absence of marked T2-hypointensity [11]. Severity of WMI was classified as mild (≤3 areas of T1 signal abnormality measuring <2 mm), moderate (> 3 areas of T1 signal abnormality measuring <2 mm or T1 signal abnormality areas measuring >2 mm but covering <5% of the cerebral hemisphere) or severe (T1 signal abnormality covering >5% of the cerebral hemisphere) [11, 17]. Cerebral strokes referred to lesions of ≥3 mm with or without diffusion restriction on diffusion weighted imaging [10]. The size of cerebral stroke was defined by its extension within the vascular territory corresponding to less than one-third, between one- and two-thirds or more than two-thirds of the territory. The severity of intraventricular haemorrhages was graded according to Papile *et al*. [18]. Subdural haemorrhages were specified by localization in relation to the tentorium cerebelli. The grade of myelination within the posterior limb of the internal capsule (PLIC) was evaluated on T1 and T2 spin-echo sequences. PLIC abnormality was defined as the absence of hyperintensity in the PLIC area both on T1 and on T2 [19]. The term 'cerebral lesions' was used for the presence of WMI or cerebral stroke. Each MRI examination was assessed by two blinded and independent neuroradiologists analysing the presence and severity of brain abnormalities including intraventricular, subdural, plexus and parenchymal cerebral haemorrhage, WMI and cerebral strokes as well as the grade of myelination within the PLIC using a scoring system described in detail below. Cohen's Kappa values for interobserver agreement were excellent ranging from 0.82 to 0.93. Therefore, the scores of the more experienced observer were used for the further analysis.

Cerebral MRI was performed in natural sleep in all neonates in clinical and haemodynamic stable conditions. Noise-protecting ear plugs and ear plug muffins were installed and immobilization of head, neck and trunk was achieved by using a special MRI vacuum mattress (RedVac Pediatric Vacuum Immobilisation, Kohlbrat & Bunz Co, Austria). During MRI examination, patients were monitored by electrocardiogram, pulse oximetry and blood

pressure under supervision of a paediatric anaesthesiologist. Five neonates with CHD underwent cerebral MRI under general anaesthesia, all others were spontaneously breathing. Healthy term neonates were all examined in natural sleep. Healthy controls were older regarding the corrected GA with a median of 42.9 weeks at the time of MRI scans compared with the corrected GA at preoperative MRI of the study patients (corrected GA 40.3 weeks, $P < 0.001$).

Neurodevelopmental assessment

Neonates with CHD were examined pre- and postoperatively in the absence of analgesic or sedative medication, by two experienced developmental pediatricians blinded towards MRI findings. The standardized assessment was modified after Prechtl and Beintema and resulted in a neurological severity score [20]. This sum score ranging from 0 to 18 is equally based on each of the following six domains: posture, general movements, tone, primitive reflexes and muscle stretch reflexes, cranial nerves and reactivity/behaviour. Asymmetries in each domain were noted.

Statistical analysis

Clinical characteristics of neonates with CHD and healthy control neonates were compared using the Mann–Whitney *U*-test and χ^2 with Fischer's exact test. Statistical comparison of birth, cardiac and perioperative variables in neonates with CHD with and without preoperative cerebral lesions was done using the Mann–Whitney *U*-test or χ^2 with Fischer's exact test. Correlations between length of hospital stay and intraoperative variables were calculated using Spearman's rank correlation. A *P* value of <0.05 was considered statistically significant. SPSS statistical package (version 20.0) was used for analysis.

RESULTS

Patient recruitment

During the study period, parents of 43 neonates with CHD requiring CPB surgery were asked for participation in the study. Recruitment was not possible due to haemodynamic instability in 1 patient, parental refusal in 8, palliative care in 1 and other reasons in 3. Therefore, 30 neonates were studied. Seventeen neonates were on continuous prostaglandin infusion during preoperative examination. Two neonates could not be scanned postoperatively as they were older than 60 days, interfering with a scan to be performed in natural sleep; both neonates had no cerebral lesions on preoperative cerebral MRI.

Magnetic resonance imaging results in healthy term neonates

Healthy term neonates were born at a median GA of 39.5 (range 37.5–41.1) weeks. MRI was acquired on a median day of 22.5 (13–33) days, corresponding to 42.9 (40.1–44.6) weeks corrected GA. MRI revealed small subdural haemorrhages in 3 patients, bilateral cysts of the plexus choroideus in 1 and a 1 × 8 mm pineal gland cyst in another infant. T1-weighted spin-echo images showed normal signal in the PLIC in 16 (80%) neonates, signal abnormality was seen in 3 (15%) neonates. In 1 neonate, T1-weighted images could not be analysed due to technical reasons. Healthy controls with myelinated WM in the PLIC region were older (median GA 43.2, range 40.1–44.6) than those without myelinated WM in the PLIC (median GA 41.5, 40.6–42.5; $P = 0.21$).

Preoperative findings in patients with congenital heart disease

Clinical findings. Cardiac diagnoses are given in Table 1. Twenty-two patients had d-TGA (73%) and 6 had a univentricular heart malformation (20%). Cardiac bypass surgery included arterial switch operation in 21 neonates (70%), Rastelli operation in 1 (3%), Norwood-type stage I palliation in 6 (20%) and complex aortic arch reconstruction in 2 (7%). Patient characteristics and data regarding birth and preoperative clinical status are summarized in Table 2.

Four neonates had a complicated preoperative clinical course and underwent MRI under general anaesthesia. Of those, 3 were resuscitated during BAS. One of these neonates showed a short tonic–clonic seizure with pathological electroencephalogram, while another presented with muscular hypertonia and had a cerebral stroke on cranial ultrasound following BAS (Patient 25 in Table 1). None of the other neonates had neurological signs.

Preoperative neurodevelopmental assessment. Preoperative neurological assessment was performed in 22 neonates at a median age of 7 (2–13) days. Results are given in Table 3. Preoperative assessment was not possible due to mechanical ventilation and/or sedation in 8 neonates, 2 of them had cerebral lesions on MRI, which was comparable with the frequency of cerebral lesions in examined patients.

Mild abnormalities were found in 82% of the neonates. Four neonates had a mild plagiocephalus. Neonates with preoperative cerebral lesions showed a significant poorer neuromotor score than neonates without cerebral lesions, most often consisting of poorer posture, muscle tone and auditive/visual behaviour (Table 3). Seventeen of the 22 (77%) neonates were treated with prostaglandin. Prostaglandin administration was not associated with worse neurological findings ($P = 0.81$).

Preoperative cerebral MRI. Preoperative cerebral MRI in neonates with CHD was acquired at a median age of 6 (1–12) days. Type and distribution of brain injury on preoperative cerebral MRI are shown in Fig. 1 and in Table 1. Cerebral lesions (WMI or stroke) occurred in 7 of 30 patients (23%) with isolated WMI in 4 patients, isolated cerebral stroke in 1 and combined WMI and cerebral stroke in 2. The severity of WMI was mild in 4 patients and moderate in 2. All cerebral strokes were small. Intracranial haemorrhages were found in 14 neonates (47%) either in the subdural space or in the choroid plexus without midline shift. Two patients had both subdural and choroid plexus haemorrhage.

All 4 neonates with a complicated clinical course showed abnormal preoperative cerebral MRI (Table 1). In 24 (80%) neonates, T1 and T2 spin-echo sequences images showed abnormal signal in the PLIC area, whereas this was only the case in 3 healthy term neonates (15%) ($P < 0.001$, Fisher's exact test).

Risk factors for preoperative cerebral lesions. Comparison of preoperative variables of neonates with and those without preoperative cerebral lesions (Table 2) revealed significantly lower preoperative transcutaneous oxygen saturation in neonates with

Table 1: Cardiac diagnosis and preoperative magnetic resonance imaging findings

Patient	Cardiac diagnosis	Preoperative magnetic resonance imaging				Preoperative neuromotor score
		Subdural haemorrhage	Plexus haemorrhage	WMI	Stroke	Total score (0–18)
1	d-TGA	–	–	–	–	2
2[a]	d-TGA	–	Yes	Moderate	–	–
3	d-TGA	–	Yes	–	–	2
4	d-TGA	–	–	Mild	–	5
5	UVH–LV	–	Yes	–	–	0
6	d-TGA	–	–	–	–	2
7	d-TGA	–	Yes	Moderate	PCA (left)	4
8	d-TGA	–	–	–	–	2
9	d-TGA	Infra	Yes	–	–	–
10	d-TGA	–	–	–	–	0
11	d-TGA	Both	–	Mild	MCA (right)	5
12	d-TGA	–	Yes	–	–	0
13	d-TGA	Infra	–	–	–	1
14	d-TGA	–	Yes	–	–	3
15	UVH–LV	–	–	–	–	0
16	d-TGA	Infra	–	Mild	–	6
17	d-TGA	Infra	–	–	–	3
18	UVH–RV	–	–	–	–	–
19[a]	d-TGA	Infra	Yes	–	–	–
20	d-TGA	–	–	–	–	1
21	UVH–RV	Infra	–	–	–	1
22	d-TGA	–	–	–	–	1
23[a]	UVH–LV	Both	–	–	–	–
24	d-TGA	–	–	–	–	2
25[a]	d-TGA	–	–	–	MCA (left)	–
26	IAA	–	–	–	–	–
27	UVH–RV	–	–	–	–	–
28	d-TGA	–	–	–	–	2
29	d-TGA	–	–	Mild	–	2
30	CoA	–	–	–	–	2

d-TGA: d-transposition of great arteries; UVH: univentricular heart; LV: left ventricle; RV: right ventricle; IAA: interrupted aortic arch; CoA: coarctation of the aorta with severe aortic arch hypoplasia; WMI: white matter injury; MCA: stroke in mid cerebral artery territory; PCA: stroke in posterior cerebral artery territory.
Left/right refers to cerebral hemispheres; supra/infra both refer to localization of the haemorrhage in relation to the tentorium cerebelli; mild/moderate refers to severity of the WMI.
[a]Neonates with resuscitation or clinical neurological symptoms.

preoperative cerebral lesions ($P = 0.03$). There was no significant difference between those neonates with and those without preoperative cerebral lesions concerning BAS, 5-min Apgar score or need for cardiac resuscitation.

Postoperative findings

Clinical findings. After surgery, no patient showed episodes of seizure or focal neurological deficits or needed to be resuscitated. Twenty patients showed postoperative arrhythmia, and 4 patients had a sepsis after surgery.

Postoperative neurodevelopmental assessment. After surgery, all the 30 neonates could be examined at median 15 (9–86) days after CPB surgery at the age of 30 (18–94) days. Median sum score on neurological examination was 2.5 (range 0–7) showing persistence of mild-to-moderate abnormalities in the majority of neonates (Table 3). Postoperative neurodevelopmental status was not different between neonates with and those without preoperative ($P = 0.55$) or postoperative cerebral lesions ($P = 0.96$).

Postoperative MRI. Postoperative MRI was performed at a median of 13 (6–30) days after surgery and at a median corrected GA of 43.2 (40.2–47.0) weeks, respectively. The spectrum of brain injuries detected on postoperative cerebral MRI is shown on Fig. 1. New intracranial haemorrhage was the predominant finding in 8 neonates (27%). Only 2 neonates (7%) manifested new cerebral lesions, both mild WMI. New cerebral strokes were not detected after surgery. Preoperative cerebral lesions persisted in 5 of 7 (71%) but did not worsen between pre- and postoperative scans. One infant developed an isolated vein of Galen thrombosis without any other cerebral lesion. Myelination in the PLIC had evolved between pre- and postoperative MRI in 10 (30%) neonates. Twelve of 28 CHD patients (43%) showed a persistence of signal abnormalities in the PLIC on T1 and T2 spin-echo sequences. This proportion was higher than that seen in controls (15%, $P = 0.05$), whose MRIs were taken at a comparable corrected GA (43.2 CHD vs 42.9 weeks in controls).

Overall, when both CHD neonates and controls were combined, the presence of a PLIC sign strongly correlated with GA at the time of the first MRI (Spearman Rho 0.64, $P < 0.001$).

Risk factors for postoperative cerebral lesions. We did not find risk factors of intraoperative variables or duration of hospital stay when comparing postoperative clinical data of neonates with and those without postoperative cerebral lesions.

Table 2: Demographic, birth and preoperative variables of neonates with congenital heart disease stratified for preoperative cerebral lesions (white matter injury or strokes)

	Total	Preoperative lesions	No preoperative lesions	*P*-value
Gender (male)	22 (73)	6 (86)	16 (70)	0.64
Age at preoperative MRI (days)	6 (1–12)	10 (5–12)	6 (1–11)	0.06
Gestational age at MRI (weeks)	40.3 (37.9–42.7)	40.9 (39.0–42.1)	40.3 (37.9–42.7)	0.64
Prenatal diagnosis of CHD	5 (17)	0 (0)	5 (22)	0.30
Gestational age (weeks)	39.3 (36.7–41.9)	39.6 (37.6–40.7)	39.1 (36.7–41.9)	0.92
Birth weight (g)	3310 (2560–4270)	3320 (2560–4270)	3330 (2660–3990)	0.51
Birth length (cm)	49.3 (46.0–54.0)	49.0 (46.0–54.0)	49.5 (47.0–53.0)	0.46
Birth head circumference (cm)	34.0 (32.0–36.0)	34.0 (33.0–36.0)	34.0 (32.0–36.0)	0.54
Apgar score 5	9 (2–10)	8 (8–10)	9 (2–10)	0.74
Arterial blood pH at birth (cord)	7.27 (7.11–7.49)	7.29 (7.21–7.49)	7.26 (7.11–7.40)	0.27
Need for nasogastric tube	26 (87)	6 (86)	20 (87)	1.00
Catecholamine support	19 (63)	4 (57)	13 (55)	0.37
Balloon atrioseptostomy	18 (60)	6 (86)	12 (52)	0.19
Low O_2-saturation (%)	65 (17–94)	46 (17–74)	65 (18–94)	**0.03**
Ventilation	22 (73)	5 (71)	17 (74)	1.00
Cardiopulmonary resuscitation[b]	1 (3)	0 (0)	1 (4)	1.00
Haematocrit (%)	42 (32–61)	42 (32–61)	42 (33–49)	0.67
Lowest mean blood pressure (mmHg)	31 (20–78)	30 (20–78)	31 (23–58)	0.56
Highest lactate (mmol/l)	5.35 (2.2–24.0)	6.0 (2.6–24.0)	5.1 (2.2–22.0)	0.77
Highest creatinine (μmol/l)	75 (34–159)	73 (59–112)	77 (34–159)	0.63
Age at surgery (days)	12 (7–62)	12 (9–19)	12 (7–62)	0.75
Aortic cross clamp time (min)	122 (90–190)	118 (98–190)	125 (90–182)	0.64
CPB time (min)	200 (123–264)	203 (158–263)	199 (123–264)	0.79
Duration of hospital stay (days)	34 (13–103)	39 (21–45)	31 (13–103)	0.36

The significant of *P*-values should be mentioned in bold.
[a]*n* (%)/total for categorical variables or median (range) for numerical variables.
[b]Cardiopulmonary resuscitation: chest compression and catecholamine administration.

Table 3: Pre- and postoperative neuromotor scores of neonates with congenital heart disease stratified for pre- and new postoperative cerebral lesions (white matter injury or strokes)

	Total Median (range)	Preoperative lesions (n = 5)[a] Median (range)	No preoperative lesions (n = 17)[a] Median (range)	*P*-value[b]
Preoperative total score (range 0–18)	2 (0–6)	5 (2–6)	2 (0–3)	**0.01**
Posture (range 0–3)	0 (0–1)	1 (1–1)	0 (0–1)	**0.01**
Movements (range 0–3)	0 (0–2)	1 (0–2)	0 (0–1)	0.27
Muscle tone (range 0–3)	1 (0–2)	1 (1–2)	1 (0–2)	0.12
Reflexes (range 0–3)	0 (0–0)	0 (0–0)	0 (0–0)	1.00
Reactivity/behaviour (range 0–3)	0 (0–2)	1 (0–2)	0 (0–1)	0.31
Auditive/visual behaviour (range 0–3)	0 (0–1)	0 (0–1)	0 (0–0)	**0.04**
	Total[c] Median (range)	New postoperative lesions (n = 2)[c] Median (range)	No new postoperative lesions (n = 26)[c] Median (range)	*P*-value[b]
Postoperative total score (range 0–18)	2.5 (0–7)	2.5 (2–3)	2.5 (0–7)	0.96
Posture (range 0–3)	1 (0–2)	0 (0–0)	1 (0–2)	0.44
Movements (range 0–3)	0 (0–2)	0 (0–0)	0 (0–2)	0.22
Muscle tone (range 0–3)	1 (0–2)	1 (1–1)	1 (0–2)	0.85
Reflexes (range 0–3)	0 (0–1)	0 (0–0)	0 (0–1)	0.69
Reactivity/behaviour (range 0–3)	0 (0–1)	0.5 (0–1)	0 (0–1)	0.41
Auditive/visual behaviour (range 0–3)	0 (0–2)	0 (0–0)	0 (0–1)	0.45

The significant of *P*-values should be mentioned in bold.
For subscores ranging from 0 to 3: scores 0 = normal, 1 = mild, 2 = moderate, 3 = very abnormal.
[a]Eight neonates could not be examined due to mechanically ventilation or sedation.
[b]Comparison between neonates with and those without preoperative and new postoperative lesions, respectively.
[c]For total score, 30 neonates were analysed; cerebral MRI was only available for 28 neonates.

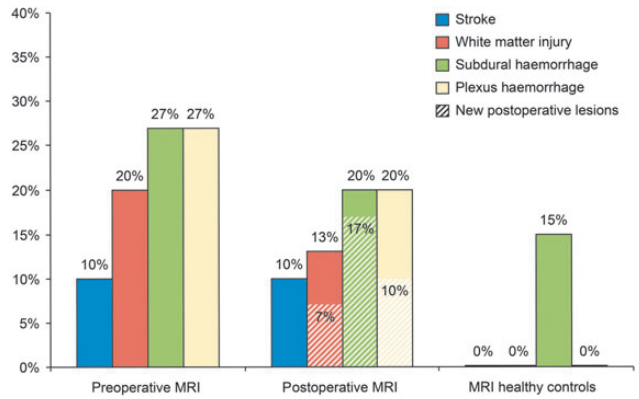

Figure 1: Morphological findings in cerebral MRI. Bar charts show the number of patients presenting subdural haemorrhage, plexus haemorrhage, white matter injury and stroke on pre- and postoperative MRI as well as the number of healthy controls presenting brain injuries. New postoperative brain injuries are presented as shaded areas. Percentage on each bar reflects the prevalence of each type of injury within the 30 patients and 20 healthy controls, respectively.

Table 4: Pre- and postoperative cerebral lesions comparing type of surgical procedure

	ASO/Rastelli procedure (n = 22)	Norwood procedure/ aortic reconstruction (n = 8)	P-value
Preoperative cerebral lesions	7	0	0.14
White matter injury	6[a]	0	0.16
Stroke	3[a]	0	0.55
CPB time (min)	193 (123–264)	208 (156–262)	0.39
Aortic cross-clamp time (min)	122 (90–190)	124 (97–163)	0.91
Postoperative cerebral lesions	1	1	0.44
White matter injury	1	1	0.44
Stroke	0	0	1

ASO: arterial switch operation.
[a]In 2 patients, both WMI and cerebral stroke were present.

Type of surgery. In order to allow a better comparison of MRI results in neonates with CHD, we analysed MRI results according to surgical procedure and underlying heart disease. We, therefore, created two patient groups, one operated by arterial switch (n = 21) and Rastelli procedure for d-TGA (n = 1) and the other group operated by the Norwood procedure (n = 6) and complex aortic arch surgery (n = 2) (Table 4). There were no differences between the two surgical procedures regarding intraoperative variables. Neonates treated by the Norwood procedure or aortic arch reconstruction had no cerebral lesions on preoperative MRI, while all cerebral lesions documented in this study on preoperative MRI were found in neonates treated by arterial switch or Rastelli procedure. Despite not reaching statistical significance, there was a trend towards significance between those groups (P = 0.14).

DISCUSSION

The main finding of our study was that preoperative cerebral MRI lesions occurred in 23% of neonates (Fig. 1) and were associated with preoperative neurological abnormalities. In addition, we could show that cerebral findings predominantly consisted of mild or moderate WMI and less frequently of cerebral strokes. The detected cerebral strokes were peripheral and small. Subdural and plexus haemorrhages occurred in 47% of neonates. After surgery, only 2 neonates developed new cerebral lesions, consisting of WMI, while in all other neonates, the preoperative lesions diminished or disappeared.

Our study confirms the findings of previous publications in which the predominant injury patterns are WMI, stroke and haemorrhages [12]. While we detected a higher rate of subdural and plexus haemorrhages than those reported in the literature [10, 12], they were not associated with higher grade intraventricular haemorrhages. Regarding the prevalence of preoperative parenchymal lesions, we found a rate of WMI (23%) similar to that reported by other studies [9, 10, 12, 21], ranging from 16 to 30%. However, the rate of stroke in our study (10%) was similar to the rate reported by Mahle *et al.* [9], but lower than that reported by other groups [11, 12]. The reason for the low rate of preoperative strokes in our study is probably multifactorial and may be associated with preoperative management and administration of BAS. In our cohort, BAS was performed in 60% of all neonates with only a trend towards a higher rate of preoperative cerebral lesions for those treated with BAS compared with those without BAS intervention. In contrast, Petit *et al.* [14] did not find an association between BAS and preoperative cerebral lesions. Therefore, the impact of BAS as a separate risk factor for preoperative brain injury remains unclear.

Interestingly, all preoperative cerebral lesions were found in patients with d-TGA. This difference, however, was not statistically significant, probably due to the small number of patients in each group.

We could identify low oxygen saturation as a risk factor for preoperative cerebral lesions, which is in line with the results of other groups reporting on neonates with d-TGA [11, 14]. A new finding in our study is that the preoperative cerebral lesions detected on MRI are correlated with the severity of neurological findings on clinical examination before surgery. Neurobehavioural abnormalities in neonates and infants prior to bypass surgery have been shown to strongly predict later neurodevelopmental impairments [22]. However, the significance of cerebral abnormalities detected on pre- and postoperative MRI for neurodevelopmental outcome has not yet been reported.

After surgery, new postoperative cerebral lesions were rare (7%) compared with other reported prevalence rates [9, 10, 12]. But it is important to consider that the definition of postoperative lesions varies among studies, some including only new lesions on postoperative studies [10, 12], whereas others report rates for newly occurring postoperative lesions or changes in preoperative existent lesions after surgery [9]. In addition, differing prevalence rates of brain injuries may be due to differences in surgical procedure, CBP strategy and patient characteristics. Importantly, there is no homogeneity in the way CPB is conducted while performing extensive arch reconstructions such as that involved in a Norwood operation with extremes of use of deep hypothermia and circulatory arrest to lesser hypothermia and selective cerebral perfusion. The fact that the incidence of postoperatively newly occurring lesions was low and that existing lesions were not aggravated by CPB surgery may indicate that the intra- and postoperative impact of the surgical intervention and postoperative course on brain injury is rather low, at least in the studied cohort.

A new MRI finding in our study was the lack of myelinated WM in both PLIC regions in 80% of all neonates before surgery

compared with 15% of the healthy controls. Healthy controls with myelinated WM in the PLIC were older compared with those controls without myelinated WM in the PLIC, however, this difference was not significant. On the other hand, healthy controls were older at the time of MRI scans compared with the age at preoperative MRI of study patients. Interestingly, when the myelination of postoperative PLIC was compared with healthy controls of comparable corrected GA, CHD patients still had a higher rate of abnormal PLIC signs than controls. The reason for these differences in the PLIC remains unclear. The absence of magnetic resonance signal from myelin in the PLIC in an infant of 40 week gestation is considered to be abnormal in term newborns [19] and is frequently found in term neonates with hypoxic-ischaemic encephalopathy [23]. However, in term neonates with hypoxic-ischaemic encephalopathy, additional brain regions such as basal ganglia and thalamus are usually affected and abnormal PLIC signs do not occur in isolation [24]. In term newborns with CHD, an abnormal brain development leading to delay of brain maturation has been described by Miller *et al.* [7], and the absence of the PLIC sign found in our cohort might reflect rather delayed myelination than hypoxic-ischaemic brain injury. Whether an abnormal PLIC could serve as a marker for future neurodevelopmental impairments in CHD patients remains to be determined [25].

Limitations of our study include the rather small sample size especially for the statistical analysis of predictive risk factors, where a regression analysis should have been performed. Another bias may be that the analysed patient group consisted of less severely affected patients, because critically ill neonates could not be included in the study due to the difficulty in obtaining an MRI scan. This may have led to a trend towards better pre- and also postoperative course associated with less severe cerebral involvement.

In conclusion, we showed that WMI is the predominant cerebral findings on preoperative MRI in neonates prior to bypass surgery, correlating with clinical neurological assessment. New postoperative lesions were rare in our cohort. The relation between neonatal MRI and clinical neurological findings and later neurodevelopmental outcome needs to be determined.

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